Approval Package for:

Application Number: 074674

Trade Name: ACYCLOVIR 200MG CAPSULES

Generic Name: Acyclovir 200mg Capsules

Sponsor: Zenith Goldline Pharmaceuticals, Inc.

Approval Date: April 22, 1997

APPLICATION 074674

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Pharmacology Review(s)				
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Application Number 074674

APPROVAL LETTER

Zenith Goldline Pharmaceuticals, Inc. Attention: Karen Rocco
140 Legrand Avenue
Northvale, NJ 07647

APR 2 2 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated May 22, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendment dated April 2, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined you Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes, in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any changes in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call you attention to 21 CFR 314.81 (b) (3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerelv yours.

(b)4 - Confidential

Business L. Sporn

Director Office of Generic Drugs

Center for Drug Evaluation and Research

APPLICATION NUMBER 074674

FINAL PRINTED LABELING

Zenith Goldin

NDC 0172-4266-60

ACYCLOVIR CAPSULES

200 mg

100 CAPSULES (White)

K

0172-4266-60 Manufactured by: ZENITH GOLDLINE PHARMACEUTICALS, INC. FT. LAUDERDALE, FL 33309 _ Zε

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NDC 0172-4266-70

ACYCLOVIR

CAPSULES

NO NEW Y

CAUTION: Federal law prohibits dispensing without

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM LIGHT AND MOISTURE

NDC 0172-4266-70

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM LIGHT AND MOISTURE

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

Store between 15° and 25°C (59° and 77°F).

Store between 15° and 25°C (59° and 77°F).

Store between 15° and 25°C (59° and 77°F).

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM LIGHT AND MOISTURE

Each Capsule Contains: Acyclovir 200 mg

NDC 0172-4266-60

Manufactured by: ZENITH GOLDLINE PHARMACEUTICALS, INC. FT. LAUDERDALE, FL 33309

0172-4266-70

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LOT: EXP.

200 mm

500 CAPSULES (White)

0197K

Each Capsule Contains: Acyclovir 200 mg

NDC 0172-4266-80

ACYCLOVIR CAPSULES

200 mg

1000 CAPSULES (White)

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

Each Capsule Contains: Acyclovir 200 mg NDC 0172-4266-80

0172-4266-80 22 z n

> LOT: EXP.

ACYCLOVIR CAPSULES

DESCRIPTION

ir is an antiviral drug for oral administration. It is chemically designated as 9-[(2-Hydroxyethoxy)methylig has the following structural formula

CeH1+NsO1

Acyclovir is a white to off-white crystaline powder with a molecular weight of 225.21, and a maximum solubility. 2.5 mg/mL at 37°C. Each capsule, for oral administration, contains 200 mg of acyclovir. In addition, each capsule or following inactive ingredients: con starch, edible black ink (black iron oxide, D&C Yellow No. 10 Aluminum Lake, No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake), gelatin, lactose mo magnesium stearale, silicon dioxide, sodium lauryl sulfate and stanium dioxide. CURINCA, PHARMACOLOGY ium Lake, FD&C Bi

Mechanism of Antiviral Ethects

Acyclovir is a synthetic putine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicelia-toster virus (VZV), Epstein-Barr virus (EBV) and cRV-1 (HSV-2), varicelia-toster virus (VZV), Epstein-Barr virus (EBV) and cRV-1 (HSV-2) and EBV is highly selective. The enzyme thymidine kinase (TK) of potenty against HSV-2 (VZV EBV and CRV-1). HSV-2 (VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV-VZV and EBV converts acyclovir inhorisophase and into tripnosphate by a number of cellular enzymes. Acyclovir triphosphate instrates with herpes simplex virus OAA polymeras and inholits viral DNA polymerase. Dut to a lessert degree. In vitro, acyclovir inhiphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular a-DNA polymerase. Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-indecide cells. Thus, acyclovir is preferentially taken up and selectively converted to the active torm. The mode of acyclovir phosphorytation in cytomogalovirus-indecide cells form by herpesvirus-indecide cells. Thus, acyclovir is not clearly established, but may involve varially induced cell knases or an unidentified viral extyme. Acyclovir is not desired with shallowed to cytomogalovirus to acyclovir in virio.

Microbiology

enzyme. Acyclovir is not enucering acutivacian in promogeneous and support of cytomagolourus to acyclovir in vitro or originations of cytomagolourus to acyclovir in vitro origination of cytomagolourus to acyclovir in vitro origination of cytomagolourus to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. For the control of the cytomagolourus origination of the cytomagolourus origination of virus in cell culture (IU_{SQ}) vary greatly depending upon the particular assay used, the cell type employed, 4 and the blooratory performing the test. If the IU_{SQ} of acyclovir against SNY-1 isolates may range form 0.02 morghm. (plaque reduction in vice and GMK cells, respectively). Using a dys-uptake method in Vero cells, 9 which gives IU_{SQ} values approximately 5-to 10-fold higher than plaque reduction in vice and GMK cells, respectively. If the IU_{SQ} against NSV-2 ranges from 0.01 morghm. to 9.9 morghm. Lighted reduction in vice and GMK cells, respectively. If the IU_{SQ} against NSV-2 ranges from 0.01 morghm. to 9.9 morghm. Lighted reduction in vice and GMK cells, respectively. If the IU_{SQ} against NSV-2 ranges from 0.01 morghm. to 9.9 morghm. The control of the co

genome of any of the human herpesvruses is not known to be sensitive to acyclovir.
Pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients.
The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients.
The pharmacokinetics of acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours. 6 times daily for 5 days, and steady-state plasma levels were administered in doses of 200 to 1000 mg every 4 hours. 6 times daily for 5 days, and steady-state plasma levels were achieved by the second day of doseing. Mean steady-state peaks and trough concentrations to licinowing the final 200 mg dose were 2.8 mcg/mt. (0.4 To 0.5 4 mcg/mt.) and 0.3 mcg/mt. (0.18 to 0.4 mcg/mt.) respectively in another uncontrolled study of 20 younger immunocompetent patients with recurrent gental herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 5 hours. 4 times daily for 5 days; the mean stady-state peak and trough concentrations were 1.4 mcg/mt. (0.68 to 1.8 mcg/mt.) and 0.55 mcg/mt. (0.14 to 1.1 mcg/mt.), respectively. In general, the pharmacokinetics of acyclovir in chiefficen is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages? Trionitis to 7 years, was 2.5 hours (range 1.59 to 3.74 hours) in a multipati-dose crossover study winer 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir was demonstrated that acyclovir is not dose proportional over the doseing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir wire 400 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir wire 400 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir wire 400 mg to

ales are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes n certain patients

capsules are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella nital Herpes Intections

Acquore capsules are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicalis) Centalia Herpes intelligent.

The severity of disease is variable depending upon the immune status of the patient, the requency and uration of episodes, and the degree of cultimaters are consistent or consistent in the degree of cultimaters. The physical, emotional and psychosocial difficulties posed by herpes infections as well as the degree of debilition, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patients' needs. Thus orally administered expicions in superior disease categories. Prix Episades (pinnary and nonprimary interions commonly known as united pental herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories. Prix Episades (pinnary and nonprimary interions commonly known as united pental herpes and pental herpes.)

Double-blind, piacebo-controlled studiess (24-23) as we demonstrated that orally administered acycloris significantly reduced the cherpes simple infection (detection) of virus in insignitions by tissue cultive) and lesion herpes varied in meltion (detection) of virus in sistens by tissue cultive) and lesion herpes varied in meltion (detection) of virus in sistens by tissue cultive) and lesion herpes varied in meltion (detection) of virus in sistens by tissue cultive) and lesion herpes varied meltion (detection) of virus in sistens by tissue cultive) and lesion hard indidease may derive less benefit than those with more severe episodes. In patients with revenue's severe episodes, in which prostation, central nervous system involvement, unrary retention or invalidity to take on medication require hospitalization and more agreesses management. Herapy may be best initiated with intravenous acyclover. According to the patient in the reverse of the control of the patients wit

recurrences in greater than 95% of patients in a study of 283 patients who received acyclowir 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects

recurrence raises not me zos pareimis showed that 11% to 61% were recurrence-tree in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated gental herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's gental herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Formic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen out-weigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of

recurrent desage in mildly affected patients. Linanswered questions concerning the relevance to humans of in wiro mulagencity studies and reproductive forcitive studies in animals given high parenteral doses of acyclovir for short periods see PRECALTIONS. Cacrineopersis. Mulagenesis, impairment of Feffithy should be borne in mind when designing long-term management for indendual patients. Discussion of these souses with patients will provide them the opportunity to weigh the potential for lockery against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation. Limited studies 31-32 have shown that there are certain patients for whom intermittent short-term treatment of recurrent experises effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences immunocompromised patients with recurrent hereps infections can be treated with either intermittent or choice suppressive through Company Company (and provided and provided

Herpes Ceter infections in a double-bind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing. Realing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation 33 in a similar double-bind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia). ³⁴

symptoms (parestinesia, dysestinesia or hyperstinesia) -Chickaspior.

In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented within 24 hours of the onset of a hypocal chickenpox rash, acyclorir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15 or 72 mp/ds depending on the age group. Treatment with acyclorir reduced the maximum number of lesions (336 vs. greater than 500, lesions beyond 500 were not counted). Treatment with acyclorir reduced the maximum number of lesions (336 vs. greater than 100, lesions beyond 500 were not counted). Treatment with acyclorir also shortened the mean time to 50% healing 71 days, vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with thever (temperature greater than 100°f) by the second day (19% vs. 5.7%). Treatment with acyclorir day (19% vs. 5.7%). Treatment with acyclory associated the antibody response to vancella-zoster vruis measured one month and one year following the fratment 35 in two concurrent double-blind, placebo-controlleds distudes, a valid in 488 an ormal patients, assez 2 to 18 years, were enrolled writinh 2.4 hours of the onset of a hypical chickenpox rash, and acyclorir via. Instantent with acyclory reduced the median maximum number of lesions (277 vs. 366), reduced the median number of vesicular lesions by the stoond day of treatment (5% vs. 40), and reduced the proportion of patients with moderate to severe inching by the third day of treatment (184 vs. 44), and addition, in both studies (883 patients signs). There were no substantial differences in VZV-specific humoral or celeilular minume of residual lesions on Day 28.93.71 There were no substantial differences in VZV-specific humoral or celeilular minume or readous lesions on Day 28.93.71 There were no substantial differences in VZV-specific humoral or celeilular minume or readous lesions on Day 28.93.71 There were no substantial differe

Diagnosis Confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital heroes, appropriate examinations should be performed to rule out other sexually transmitted diseases. White outaneous lesions associated with herpes simplex and vancella-zoster infections are often characteristic, the finding of multimucleated grant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis 39 Multimucleated gain cells in smears do not distinguish varicella-zoster from herpes simplex infections CONTRAINDICATIONS Acytow'ris contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation WARHINGS

Acyclovir capsules are intended for oral ingestion only. PRECAUTIONS

General Acyclovir has caused decreased spermatopenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS, Carcinopenesis, Mutagenesis, Impairment of Fertility). The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION). Exposure of herpes simples and variotical societies to acyclovir and clinical to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *invitor* ansensitivity of herpes simples or variotical zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARIMACOLOCY, Microbiology). Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy. Caution should be exercised when administering acyclovir patients receiving potentially epiphotoxic agents since this may increase the risk of real dysfunction. Information for Patients

Patients are instructed to consult with their physician if they expenence severe or troublesome adverse reactions, they become pregnant or intent to become pregnant, they winned to breasteed while taking orally administered acyclovir, or they have any other questions.

Genital Hernes Intections

Genital therpses is a sexually transmitted disease and patients should avoid intercourse when visible tessons are present because of the risk of infecting intimate partners. Acyclovir capsules are for oral ingestion only. Medication should not be exceeded Acyclovir does not eliminate busine through the properties of the risk of infecting intimate partners. Acyclovir capsules are for oral ingestion only. Medication should not be exceeded Acyclovir does not eliminate busine through control the oral properties of the properties of

patents. Ireatment was usual to the control of the

increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of vancella-zoster infections in immunocompromised patients.

Original patients:

Origi

2 other locs in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at a concentration of the concentratio

Ann on

levels). There was a statistically significant decrease in the group mean numbers of corpora tules total implantation sates and live februses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live februses and implantation sates at 12.5 implaydus and 25 implaydus y s. The intravenous administration of 100 mg/bg/day a dose inview to cause obstructive nepholopish in rabbilis caused a significant increase in februse prosphisms and a corresponding decrease in litter size (pissma levels were not ineasured). However, at a maximum tolerated intravenous dose of 50 mg/bg/day in abbits (35 to 106 times human levels) in ording-februse reproductive effects were observed intraventional doses of 80 or 320 mg/kg/day accidion igners to rats to 6 and in onthis, respectively, caused restrictival arrophy. Plasma levels were not ineasured in the one-month study and were 24 to 48 times human levels in the six-month study Testification was referred to 30 acros stoates: intravenous doses of 100 and 200 mg/kg/day acciding even to dogs for 31 days caused aspermation was verted at 30 acros stoates: intravenous doses of 100 and 200 mg/kg/day acciding even to dogs for 31 days caused aspermation was verted at 300 mg/kg/day they were 159 to 317 times human levels. No testicious rationerabilities were 47 to 94 times human levels while at 200 mg/kg/day they were 159 to 317 times human levels. No testicious rationarialities were seen in dogs given 50 mg/kg/day to 10 one month 121 to 41 times human levels).

Pregnancy Teratogenic Effects: Pregnancy Category C

Instalganie Effect: Pregonacy Calegory C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbot (50 mg/kg/day, s.c. and iv.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18. 16 and 106, and 11 and 22 imms, respectively, human levels, or any or analysis of the second control o

Account concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels 4344. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/hg/day. Quation should be exercised when acyclovir is administered to a nursing

Satety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied ADVERSE REACTIONS

Herpes Simplex Short-Term Administration

Short-Fern Administration
The most frequent adverse events reported during clinical trails of treatment of gential herpes with orally administered acyclovir were nausea and/or vomining in 8 of 288 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomining occurred in 2 of 287 (0.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomining occurred in 2 of 287 (0.7%) and indexed where events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrinea, diszeness, andexes, latique, edema, skin rash, leg pain, inguinal adenopathy, inedication taste and sore throat Long-Tern Administration
The most trequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were inausea (4.8%), diarrine (2.4%), headache (1.9%) and rash (1.7%) in Line 599 control patients receiving intermittent treatment of recurrences with acyclovir of 1 year reported darrines (2.7%), nausea (4.4%), headache (2.2%) and rash (1.5%).
The most trequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 cares were headache (1.5%), and nariset listed (6.8%). Adverse

of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Adverse events reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

Herpes Zoster
The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclowin 5 times daily for 7 to 10 days in 329 patients were: malaise (11.5%), hausea (8.0%), headache (5.9%), vonning (2.5%), disrribantation (9.9%). The 229 disclore forecopients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarriba (0.3%) and constipation (2.4%).

Chickenpox
The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarribea (3.2%), abdominal pain (6.6%), rash (6.6%), commiting (6.6%), and illatulence (0.4%). The 498 patients receiving placefor properties disarribea (2.2%), fatulence (0.8%) and insommia (0.4%).

Observed During Clinical Practice
Based on clinical practice experience in patients treated with oral acyclowr in the U.S. spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include.

Fever, headache, pain, peripheral edema, and rarely, anaphylaxis

infusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older

adults :

Digestive
Digest

opecia, pruritus, rash, urticaria Special Senses

Visual abnormalities Urogenilal

OVERDOSAGE

OVERDOSAGE
Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects
Precipitation of acyclovir in renal tubules may occur when the solipbility (2.5 mg/m.) in the intratibular fluid is exceeded. Renal
lessons considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species
rats treated with v. and r.g. doses of 20 mg/kg/dgy for 12 and 31 days, respectively, and as c. doses of 100 mg/kg/dgy for 13 days; and dogs at it doses of 100 mg/kg/dgy for 31 days. A 6 hour
hemofullysis results in a 05% defensive in plasma according on the precipitation of the precipitation of the control of the

DOSAGE AND ADMINISTRATION
Treatment of Initial Genital Hurges
200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days
Chronic Suppressive Therapy for Recentered Disease
400 mg (two 200 mg capsules) 2 times daily for up to 12 months. followed by re-availation. See INDICATIONS AND USAGE and
PRECAUTIONS to crossiderations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included
doses ranging from 200 mg a times daily to 200 mg 5 times daily to 200 mg 5 times daily or 5 days. Therapy should be initiated at the earliest sign or
symptom (profine) of recurrence.
Acute Treatment of Herpas Zoster
800 mg (flow 200 mg capsules) every 4 hours orally 5 times daily for 7 to 10 days.
Treatment of Chrickenpox
Treatment of Chrickenpox

Children (2 years of age and older

20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickengox

Adults and children over 40 kg 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy Patients with Active or Thomaic Renal Impairment Comprehensive pharmacolinetic studies have been completed following infravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes soster indications.

Normal Dosage Regimen	Creatinine Clearance (mL/mm/1.73 m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis

for patients who require hemodialysis the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours.

This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore the patient's dosing schedule should be adjusted so that an additional dose is administered after each dulysis 45.46.

dose appears to be necessary after adjustment of the dosing interval 47.4

NOW SUPPLEU

Acytowic classifies are available as white opaque hard gelatin capsules, spin printed "4266" on the cap and "200" on the load, containing 200 mg acytowic packaged in bothes of 100, 500 and 1000 capsules

PHARMACIST Disposers in a high high-resistant container as defined in the USP. Use child-resistant closure (as required. PROTECT FROM LIGHT AND MOISTURE Store between 15° and 25°C 15° and 77°F;

CAUTION Federal law prohibits dispensing without prescription.

- NEWCES Of Bren JJ. Campoli-Richards DM. Acyclovir an updated review of its antiviral activity, pharmacokinetic properties, and therapeutic efficacy. *Origis* 1989;37:233-309. Littler E. Zeuthen J. McBride AA, et al. Identification of an Epstein-Barr virus-coded thyrmdine kinase. *EMBO J*. 1986;3(6):1999-1966.
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- perplacation by 0-1/2-mortane reads a innominor on nerges simplex virus-induced DNA polymerase activity and viral DNA perplacation by 9-1/2-mortane provided in the provided provided
- 11447-11451
 McGurf PV, Shaw JE, Elion GB, et al. Identification of small DNA fragments synthesized in herpes simplex virus-infected cells in the presence of acyclovir. Antimicrob Agents Chemother 1984:25-507-509
 Barry DW, Bim MR: Antiviral drugis' acyclovir. In: Turner P. Shand DG ets. Recent Advances in Clinical Pharmacology, et 3. New York, Churchik Leingstone; 1983: chap 4. DeClerca E. Comparative ethicacy of antimerpes drugs in different cell lines. Antimicrob Agents Chemother, 1982;21: 661-663.

- 661-663
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MANUFACTURED BY ZENITH GOLDLINE PHARMACEUTICALS, INC. FT_LAUDERDALE, FL_33309

ACYCLOVIR CAPSULES

APPLICATION NUMBER 074674

CHEMISTRY REVIEW(S)

ADDENDUM

ANDA # 74-674

REVIEW # 3

NAME AND ADDRESS OF APPLICANT
Zenith Goldline Pharmaceuticals, Inc.
140 Legrand Avenue
Northvale, NJ 07647

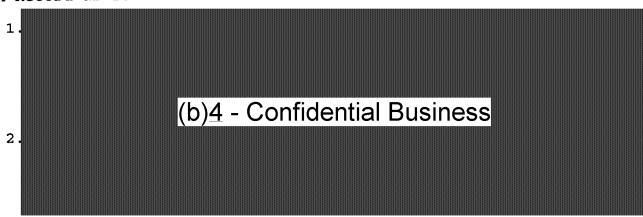
PROPRIETARY NAME N/A

NONPROPRIETARY NAME
Acyclovir Capsules 200 mg

AMENDMENT DATE: April 2, 1997

COMMENTS

The applicant indicated that two minor changes were made to the Master Batch Record as follows:



In support of the changes, the firm submitted release data for their first validation batch of drug product demonstrating conformance to specifications.

CONCLUSIONS AND RECOMMENDATIONS

The changes submitted are minor and should have no significant impact on the drug product. The application may be Approved.

REVIEWER:
Glen Jon Smith

DATE COMPLETED:
April 9, 1997





ANDA APPROVAL SUMMARY

ANDA: 74-674 DRUG PRODUCT: Acyclovir USP

FIRM: Zenith DOSAGE FORM: HG Capsule STRENGTH: 200 mg

140 Legrand Avenue Northvale, NJ 07647

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 251) in original submission, and Section 306(k) certification in New Correspondence, 7/13/95.

EIR acceptable for drug product manufacturer and drug substance manufacturer, 2/23/96. Pre-Approval update requested, 2/14/97.

Facilities included:

Manufacturing, testing, packaging, labeling and stability testing:

Zenith Laboratories, Inc. 140 LeGrand Avenue Northvale, NJ 07647

Drug Substance Manufacturer:

(b)4 - Confidential Business

Testing:

(b)4 - Confidential Business

BIO STUDY:

Bioequivalence study conducted on the 200 mg capsules Lot #ND-244, batch size (b)4 - apsules was found acceptable by the Division of Bioequivalence per K. Dhariwal, 5/9/96.

In-vitro dissolution study for 200 mg capsules was found acceptable.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substance is compendial. Methods for Acyclovir drug product were found to be acceptable by the Philadelphia District Laboratory, 6/4/96. Laboratory description of dosage form was the same as firm's.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability for the following included:

Dosage Lot # 200 mg ND-244

Batch Size (h)4 -

Sample 100's 500's 1000's Test Conditions
40°C/75% RH/3 months
25° - 30°C/3 months

Container/Closure system:

(b)4 - Confidential Business

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months based on accelerated data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, J. White, 2/18/97.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio batch: 200 mg product, Lot #ND-244, batch size (b)4 - capsules, stability data included.

(b)4 - Confidential satisfactory, N. Gregory, 2/7/97, no amenaments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Executed batch record for the 200 mg x (b)4 - patch Lot #ND-244 (bio/stability batch) included. A blank batch record was submitted in the application for (h)4 - Confidential All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST:

SUPERVISOR

/S/

DATE: 1 and 6, 1997

DATE: 3/7/97



Food and Drug Administration Center for Drug Evaluation and Research Office of Generic Drugs

Chemistry Division II - Branch VII Abbreviated New Drug Application Review

- CHEMISTRY REVIEW NO. 3 1.
- ANDA # 74-674 2.
- NAME AND ADDRESS OF APPLICANT 3. Zenith Laboratories, Inc. 140 LeGrand Avenue Northvale, New Jersey 07647
- LEGAL BASIS FOR SUBMISSION 4. ZOVIRAX® Capsules, 200 mg/capsule Burroughs Wellcome Co. 3030 Cornwallis Road Research Triangle Park, NC 27709

Acyclovir is covered by Patent #4199574, Expiration Date April 22, 1997. The firm certified that they will market the product following expiration of the patent. An exclusivity for the treatment of varicella infections expired February 26, 1995.

5. SUPPLEMENT(s) N/A

- 6. PROPRIETARY NAME N/A
- 7. NONPROPRIETARY NAME Acyclovir USP
- 8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
- AMENDMENTS AND OTHER DATES: 9.

Firm:

- Original submission. 5/22/95
- New Correspondence Response to Agency's request 7/13/95 of 7/10/95.
- Amendment Response to Agency's Incomplete 1/12/96 Bioequivalence letter of 11/13/95.
- Notification of Transferral of ANDA 3/11/96
- Amendment Response to Agency's letter of 12/12/95. 6/13/96
- 1/29/97 Amendment - Response to Agency's facimile of 1/16/97.

FDA:

- 7/10/95 Receipt acknowledged. Request for original copy of 306(k) certification.
- Issuance of Incomplete Bioequivalence letter. 11/13/95
- 12/12/95 Issuance of Not Approvable letter.
- Issuance of Acknowledgment of Transfer.
- 5/3/96 5/14/96 Issuance of Bioequivalence No Further Questions letter.
- 1/16/97 Facimile Minor Issued.
- 10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC Antiviral Rx
- RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

- 13. <u>DOSAGE FORM</u>
 HG capsule for oral administration
- 14. <u>POTENCIES</u> 200 mg/capsule
- 15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP $C_8H_{11}N_5O_3$; M.W. = 225.21 CAS [59277-89-3]

- 9-[(2-Hydroxyethoxy)methyl]guanine.
- 2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257° . LD₅₀ in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS

10/30/95 - Chemistry review #1, G.J. Smith.

11/1/95 - Labeling review, L. Golson.

11/4/95 - Bioequivalence review, K. Dhariwal.

ANDA #74-674 Review #2 Page 3

5/6/96 - Bioequivalene review, K. Dhariwal.

8/26/96 - Labeling review, J. White.

12/6/96 - Chemistry review #2, G.J. Smith.

2/18/97 - Labeling review, J. White.

17. COMMENTS

The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory, J.White, 2/20/97.

The Division of Bioequivalence found the drug product equivalent, K. Dhariwal, 5/6/96.

Acceptable EIR issued by the Office of Compliance, 2/23/96. Update requested 2/14/97.

Methods validation found satisfactory, with minor revision recommended, Philadelphia District Laboratory, 6/4/96.

(b)4 - for drug substance was found satisfactory, N. Gregory, 2/7/97 updated.

- 18. <u>CONCLUSIONS AND RECOMMENDATIONS</u>

 The application may be granted Tentative Approval status.
- 19. REVIEWER: DATE COMPLETED:
 Glen Jon Smith March 4, 1997.

APPLICATION NUMBER 074674

BIOEQUIVALENCE REVIEW(S)

Zenith Goldline Pharmaceuticals
Attention: Arthur Hurwitz
140 Legrand Ave
Northvale NJ 07647

MAY 1 4 1996

Dear Sir:

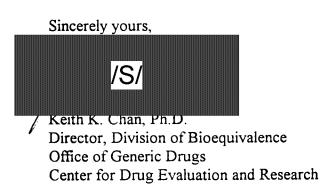
Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules USP, 200 mg.

- 1. The Division of Bioequivalence has completed its review and has no further questions at this time.
- 2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be done in 900 mL of water at 37°C using apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

Not less that be of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.



OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA # 74-674 SPONSOR: Zenith Laboratories, Inc.

DRUG: Acyclovir

DOSAGE FORM: Capsule STRENGTHS/(s):200 mg

TYPE OF STUDY: Single dose; Fasting and Food

STUDY SITE: PharmaKinetics Laboratories, Baltimore, MD 21201

STUDY SUMMARY: Fasting Study: Thirty-two subjects entered the study. Five subjects did not return for phase II. The 90% confidence intervals for $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} were 85-107%, 87-106%, and 86-109% respectively. AUC_{0-t} and AUC_{0-inf} for the test product were 5% and 4% lower than the respective estimates for the reference product. The C_{max} of test product occurred 12 minutes later and was 3% lower compared to reference product.

Food Study: Eighteen subjects entered the study. Three subjects voluntarily withdrew and one subject was withdrawn because at entry of phase III, his BP readings were 160/102. The test/reference ratios for mean AUC_{0-t} , AUC_{0-inf} , and C_{max} were 0.96, 0.96, and 0.94 respectively. The mean C_{max} for test product was 6% lower than that of the reference product and occurred 7 minutes later.

DISSOLUTION: The dissolution testing was done using FDA method. At 30 min., 10 test capable dissolved less than (b)4 - Confidential. However, these results pass the acceptance critical average of 12 units (92.8%) is equal to or greater than (b)4 - and no unit is less than (b)4 - The results of dissolution tests are acceptable.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II
INITIAL: Confidential DATE 5/10/96
Connidential
BRANCH CHIEF: Shriniwas G. Nerurkar, Ph.D., BRANCH: II
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DIRECTOR C
OFFICE OF GENERIC DRUGS: Roger L. Williams, M.D.
INITIAL: DATE

Acyclovir

200 mg Capsule ANDA #74-674

Reviewer: Kuldeep R. Dhariwal

File name: 74674SD.196

Zenith Laboratories, Inc.

140 Legrand Avenue Northvale, NJ 07647 Submission Date: January 12, 1996

Response to Review of Bioequivalence Study and Dissolution Data

Background:

Zenith Laboratories previously submitted a single-dose in vivo bioequivalence study under fasting conditions and dissolution data comparing its acyclovir capsules, 200 mg with Burroughs Wellcome's Zovirax® capsules, 200 mg. Each dose consisted of 400 mg (2 capsules) of either the test or reference product (Filename: 74674SD.595; submission date: May 22, 1995). The bioequivalence study conducted by the firm under fasting conditions and dissolution data were found acceptable. The ANDA was, however, incomplete because the firm had not submitted the food study. The firm submitted the food study as amendment on January 12, 1996 which was received by the Division of Bioequivalence on January 16, 1996. The study (amendment) was assigned to this reviewer on April 8, 1996, who started the review on April 10, 1996.

Bioavailability of Acyclovir Capsules, 200 mg under Fed Conditions:

A. Objective: The objective of this study was (1) to compare the acyclovir plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of a marketed reference product, after the standard meal and (2) to compare the acyclovir plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the test formulation, after an overnight fast.

B. Study Sites and Investigators:

Clinical Site: (b)4 - Confidential Business

Medical Director: (h) 4 - Confidential Business
Protocol #10848 "Bioavailability of acyclovir capsules, 200 mg:
Effect of food study" was approved by the National Institutional
Review Board for (h) 4 - Confidential Business
Consent Form: A copy of volunteer informed consent form used in

the study is given on page 38, vol. 2.1.
Study Dates: Period I January 31 - Feb. 2, 1995

Period II February 7 - Feb. 9, 1995

Period III February 14 - Feb. 16, 1995

Analysis Dates: November 14, 1995 to December 7, 1995

C. Study Design:

A randomized, single-dose, six-sequence, three-way crossover study design was used. The study was executed in three periods with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from at least 12 hours before until at least 24 hours after drug administration, each phase. The subjects (who completed the study) were assigned as follows:

Subject #	Period I	Period II	Period III
1,12	Α	В	С
2,7,15	С	В	A
3,11,16	A	С	В
4,17	В	С	A
10,13	С	A	В
6,14	В	A	С

A = Acyclovir Capsules, 2 X 200 mg following a standard meal, Zenith Laboratories. Inc.: Lot #ND-244; Lot size: Theoretical Yield: (b)4 - Confidential Business Expiration Date: 8/1995; Manufacture Date: 8/94; Assay: 99.3%; Uniformity of dosage units: 97.6%.

B = Zovirax® Capsules, 2 X 200 mg following a standard meal, Burrough Wellcome Co.; Lot #4N2584; Expiration Date: 3/97; Assay: 99.9%; Uniformity of dosage units: 98.4%.

C = Acyclovir Capsules, 2 X 200 mg following an overnight fast, Zenith Laboratories, Inc.; Lot #ND-244

Formulation: See earlier review (Nov. 4, 1995) for fasting study.

Lot numbers of drug products administered in this study were the same as those used for the fasting study.

D. Subject Selection:

Eighteen healthy male subjects were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- male, healthy, 18-50 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from this study based on the following criteria:

- history of asthma, chronic bronchitis, herpes, hypertension, cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to acyclovir or to related drugs

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days (excluding contraceptives) or OTC medications (excluding OTC ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenzes, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers® at 0 (predose), 0.33,0.67,1,1.33,1.67,2,2.5,3,3.5,4,5,6,8,10,12,14,16 and 24 hours postdose. Samples were centrifuged within 15 minutes of acquisition. The plasma was transferred to prelabeled polypropylene tubes and promptly frozen at -20°C.

F. Analytical Methods:

(b)4 - Confidential Business

(b)4 - Confidential Business

G. Pharmacokinetics/Statistical Analysis:

The area under the plasma concentration versus time curve was calculated using the linear trapezoidal rule from the zero time point to the last quantifiable concentration. The area under the plasma concentration versus time curve from zero to infinity was calculated by adding C_t/K_{elm} to AUC_{0-t} where C_t is the last quantifiable concentration and Kelm is the elimination rate constant. The maximum observed plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were obtained by inspection. The terminal elimination rate constant was obtained from the slope of the line, fitted by linear least squares regression, through the terminal points of the log(base e) of the concentration versus time plot for these points. The half-life was calculated by the equation $T_{y} = 0.693/K_{elm}$. The statistical analyses were performed using SAS software. The calculations for the 90% confidence interval about the ratio of the mean test value to mean reference value and for the power of the ANOVA to detect a 20% difference from the reference mean were performed using the LSMEAN values and standard error of estimate values as generated by SAS. The ratios of geometric means and the 90% confidence intervals of the log (base e) transformed data were calculated for AUC_{0-t} , AUC_{0-inf} , and C_{max} .

H. Results:

1. Clinical:

Eighteen subjects entered the study. Subject #18 failed to return after completing period I, subject #5 and 9 did not return for

period III. Subject #8 was withdrawn from the study by the physician because of increased blood pressure measurements. The plasma samples from fourteen subjects who completed the study were assayed for acyclovir. Clinical vital signs were measured at 0,4 and 24 hours. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period III. Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result		
1	Blood, RBC/HPF in urine		
17	Blood, RBC/HPF in urine		

Adverse events:

Following six subjects experienced adverse events during the study. All events were mild in severity.

Subject #	Period	Product	Sign/Symptom
6	III	Test(fasted)	1 centimeter raised pruritic bump left lateral elbow
8	III	Test(fasted)	sore throat; increased blood pressure
10	II	Test(fed)	headache, increased diastolic blood pressure
11	II	Test(fed)	headache
16	III	Ref(fed)	cold symptoms
17	II	Test(fasted) Test(fed)	lightheaded, headache 1 pruritic hive right deltoid

^{*} Self-administered 1 tablet of Advil 200 mg

Deviations in the study:

There was one deviation in scheduled phlebotomy time. A deviation was defined as greater than 5% of the time since dosing for samples up to 10 hours, and greater than 30 minutes for samples thereafter. For subject #6 in period I (reference-fed) the 20 minute sample was delayed by 4 minutes. Actual time was used for AUC calculations.

Subject 1, period 2, 24 hour samples was not received by the analytical lab from the clinic.

Reassays:

Of the 797 samples assayed, 20 samples were reassayed. Following samples were reassayed for the reasons shown against them:

<pre># of samples</pre>	Reason for reassay
5	Integrator malfunction
12	Chromatographic interference
2	Anomalous value
1	Value for predose sample

2. Analytical:

